PALM INTRANET

Day : Friday
Date: 4/23/2004

Time: 10:27:01

Inventor Name Search

Enter the **first few letters** of the Inventor's Last Name.
Additionally, enter the **first few letters** of the Inventor's First name.

Last Name	**First Name**	
Isner	Jeffrey	Search

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(BUSCHMANN-IVO-R$.IN.).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	2

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Search History

DATE: Friday, April 23, 2004 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; THES=ASSIGNEE; PLUR=YES; OP=AND			
L11	Buschmann-Ivo-R$.in.	2	L11
L10	L9 and (ischemia or ischemic)	0	L10
L9	Schafer-Wolfgang.in.	64	L9
L8	L7 not L6	26	L8
L7	(angiopoietin-1 or angiopoietin-2 or (FLT-3 adj ligand) or SCF-1) same (ischemic or ischemia)	31	L7
L6	L5 and (therapeutic adj angiogenesis)	106	L6

h e b b cg b e e ch

L5	L4 and L3	440	L5
L4	(mammal or patient or subject) same (ischemia or ischemic)	13877	L4
L3	L2 and (angiogenesis)	651	L3
L2	(ischemia or ischemic) same (VEGF or GM-CSF or SCF or SDF-1 or G-CSF or M-CSF angiopoietin or FLT-3)	760	L2
L1	Isner-Jeffrey-M$.in.	29	L1

END OF SEARCH HISTORY

h e b b cg b e e ch

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### Status: Path 1 of [Dialog Information Services via Modem]

### Status: Initializing TCP/IP using (UseTelnetProto 1 ServiceID pto-dialog)
Trying 31060000009999...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ******** HHHHHHHH SSSSSSSS?
### Status: Signing onto Dialog
 ********
ENTER PASSWORD:
 ******** HHHHHHHH SSSSSSSS? ********
Welcome to DIALOG
### Status: Connected


Dialog level 04.05.14D

Last logoff:  22apr04 08:42:21
Logon file001 23apr04 14:46:20
           *** ANNOUNCEMENT ***
                    ***
--File 654 - US published applications from March 15, 2001 to the
present are now online.  Please see HELP NEWS 654 for details.

                    ***
--File 581 - The 2003 annual reload of Population Demographics is
complete. Please see Help News581 for details.

                   ***
--File 990 - NewsRoom now contains February 2003 to current records.
File 992 - NewsRoom 2003 archive has been newly created and contains
records from January 2003. The oldest months's records roll out of
File 990 and into File 992 on the first weekend of each month.
To search all 2003 records BEGIN 990, 992, or B NEWS2003, a new
OneSearch category.
                    ***
--Connect Time joins DialUnits as pricing options on Dialog.
See HELP CONNECT for information.
                    ***
                    ***
--SourceOne patents are now delivered to your email inbox
as PDF replacing TIFF delivery. See HELP SOURCE1 for more
information.
                    ***
--Important Notice to Freelance Authors--
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NEW FILES RELEASED
***AeroBase (File 104)
***DIOGENES: Adverse Drug Events Database (File 181)
***World News Connection (File 985)
***Dialog NewsRoom - 2003 Archive (File 992)
***TRADEMARKSCAN-Czech Republic (File 680)
***TRADEMARKSCAN-Hungary (File 681)
***TRADEMARKSCAN-Poland  (File 682)
                    ***
UPDATING RESUMED
                    ***
RELOADED
***Medline (Files 154-155)
***Population Demographics -(File 581)
***CLAIMS Citation (Files 220-222)

REMOVED
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      >>> Enter BEGIN HOMEBASE for Dialog Announcements <<<
      >>>    of new databases, price changes, etc.      <<<
                     ****
KWIC is set to 50.
HILIGHT set on as '*'
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* ALL NEW CURRENT YEAR RANGES HAVE BEEN * * *
* * * INSTALLED   * * *
*

File   1:ERIC 1966-2004/Mar 31
       (c) format only 2004 The Dialog Corporation

      Set  Items  Description
      ---  -----  -----------
Cost is in DialUnits
?b 155, 5, 73
       23apr04 14:46:30 User259876 Session D613.1
            $0.31    0.089 DialUnits File1
     $0.31  Estimated cost File1
     $0.03  TELNET
     $0.34  Estimated cost this search
     $0.34  Estimated total session cost   0.089 DialUnits


SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R) 1966-2004/Apr W3
        (c) format only 2004 The Dialog Corp.
*File 155: Medline has been reloaded. Accession numbers
have changed. Please see HELP NEWS 154 for details.
  File   5:Biosis Previews(R) 1969-2004/Apr W2
        (c) 2004 BIOSIS
  File  73:EMBASE 1974-2004/Apr W3
        (c) 2004 Elsevier Science B.V.

      Set  Items  Description
      ---  -----  -----------
?s (ischemic or ischemia) (s) (mammal or rodent or primate or mouse or rat or patient)
          280889  ISCHEMIC
          334194  ISCHEMIA
          139077  MAMMAL
           81321  RODENT
           57594  PRIMATE
         1509348  MOUSE
         2738427  RAT
         3240533  PATIENT
      S1   81914  (ISCHEMIC OR ISCHEMIA) (S) (MAMMAL OR RODENT OR PRIMATE
                  OR MOUSE OR RAT OR PATIENT)
?s s1 and (angiogenesis)
           81914  S1
           63941  ANGIOGENESIS
      S2     772  S1 AND (ANGIOGENESIS)
?s s2 and (VEGF)
             772  S2
           27761  VEGF
      S3     318  S2 AND (VEGF)
?s s3 not py>1998
             318  S3
         7961134  PY>1998
      S4      66  S3 NOT PY>1998
?rd
...examined 50 records  (50)
...completed examining records
      S5      31  RD (unique items)
?t s5/3,k/all
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5/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14289151 PMID: 10193309

The vascular endothelial growth factor family; proteins which guide the development of the vasculature.

Achen M G; Stacker S A
Angiogenesis Laboratory, Ludwig Institute for Cancer Research, Royal Melbourne Hospital, Victoria, Australia. Marc.achen@ludwig.edu.au

International journal of experimental pathology (ENGLAND) Oct 1998, 79 (5) p255-65, ISSN 0959-9673 Journal Code: 9014042
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The development of the vascular tree during embryogenesis involves vasculogenesis, *angiogenesis* and tissue-specific differentiation of endothelium which gives rise to many different vessel types. These processes are physiologically complex and are therefore difficult to study in vitro. However, the discovery of endothelial cell-specific receptors and cognate ligands has led to the generation of transgenic and knockout *mouse* models which have shed light on the molecular mechanisms that regulate the development of blood and lymphatic vessels during embryogenesis. Such *mouse* models have demonstrated that members of the vascular endothelial growth factor (*VEGF*) family of proteins and the *VEGF* receptors are critical regulators of vasculogenesis, *angiogenesis* and endothelial cell differentiation. The availability of purified *VEGF* family members and of inhibitors of these growth factors may provide a means to modulate blood vessel growth for the treatment of cancer, retinopathies and diseases of *ischemia*.

5/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14161939 PMID: 9860779

Gene therapy for myocardial *angiogenesis*: initial clinical results with direct myocardial injection of phVEGF165 as sole therapy for myocardial ischemia.

Losordo D W; Vale P R; Symes J F; Dunnington C H; Esakof D D; Maysky M; Ashare A B; Lathi K; Isner J M
Departments of Medicine, Biomedical Research, Surgery, and Anesthesiology, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Mass 02135, USA.

Circulation (UNITED STATES) Dec 22-29 1998, 98 (25) p2800-4, ISSN 0009-7322 Journal Code: 0147763
Document type: Case Reports; Clinical Trial; Clinical Trial, Phase I; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Gene therapy for myocardial *angiogenesis*: initial clinical results with direct myocardial injection of phVEGF165 as sole therapy for myocardial ischemia.

BACKGROUND: We initiated a phase 1 clinical study to determine the safety and bioactivity of direct myocardial gene transfer of vascular endothelial growth factor (*VEGF*) as sole therapy for patients with symptomatic myocardial *ischemia*. METHODS AND RESULTS: *VEGF* gene transfer (GTx) was performed in 5 patients (all male, ages 53 to 71) who had failed conventional therapy; these men had angina (determined by angiographically documented coronary artery disease). Naked plasmid DNA encoding *VEGF* (phVEGF165) was injected directly into the *ischemic* myocardium via a

mini left anterior thoracotomy. Injections caused no changes in heart rate (pre-GTx=75+/-15/min versus post-GTx=80+/-16/min...

... Ventricular arrhythmias were limited to single unifocal premature beats at the moment of injection. Serial ECGs showed no evidence of new myocardial infarction in any *patient*. Intraoperative blood loss was 0 to 50 cm3, and total chest tube drainage was 110 to 395 cm3. Postoperative cardiac output fell transiently but increased...

... 03). Postoperative left ventricular ejection fraction (LVEF) was either unchanged (n=3) or improved (n=2, mean increase in LVEF=5%). Objective evidence of reduced *ischemia* was documented using dobutamine single photon emission computed tomography (SPECT)-sestamibi imaging in all patients. Coronary angiography showed improved Rentrop score in 5 of 5 patients. CONCLUSIONS: This initial experience with naked gene transfer as sole therapy for myocardial *ischemia* suggests that direct myocardial injection of naked plasmid DNA, via a minimally invasive chest wall incision, is safe and may lead to reduced symptoms and improved myocardial perfusion in selected patients with chronic myocardial *ischemia*.

5/3,K/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14132939 PMID: 9828156
Increased expression of KDR/Flk-1 (VEGFR-2) in murine model of ischemia-induced retinal neovascularization.
Suzuma K; Takagi H; Otani A; Suzuma I; Honda Y
Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, 606, Japan.
Microvascular research (UNITED STATES) Nov 1998, 56 (3) p183-91, ISSN 0026-2862 Journal Code: 0165035
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Although the vascular endothelial growth factor (*VEGF*)/*VEGF* receptor system plays a critical role in the pathogenesis of *ischemic* retinal neovascular diseases such as diabetic retinopathy, regulation of *VEGF* receptor expression in *ischemic* retina has not been fully investigated in vivo. Accordingly, we studied the regulation of Flt-1 (VEGFR-1) and KDR/Flk-1 (VEGFR-2) expression in a *mouse* model of *ischemia*-induced retinal neovascularization. Immunohistochemistry for Flt-1 and KDR/Flk-1 revealed that, in hypoxic retina, the immunoreactivity of KDR/Flk-1 was increased in...

... neovascular retina of hypoxic animals than in control animals. We suggest that the increased expression of KDR/Flk-1 in vascular cells might potentiate the *VEGF*-mediated *angiogenesis* that accompanies many *ischemic* retinal diseases.

5/3,K/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14054003 PMID: 9751672
Endothelium-dependent relaxation of collateral microvessels after intramuscular gene transfer of vascular endothelial growth factor in a *rat* model of hindlimb *ischemia*.
Takeshita S; Isshiki T; Ochiai M; Eto K; Mori H; Tanaka E; Umetani K; Sato T
Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan. stake@blue.ocn.ne.jp
Circulation (UNITED STATES) Sep 29 1998, 98 (13) p1261-3, ISSN

0009-7322 Journal Code: 0147763
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Endothelium-dependent relaxation of collateral microvessels after intramuscular gene transfer of vascular endothelial growth factor in a *rat* model of hindlimb *ischemia*.

BACKGROUND: Recent investigations have demonstrated the ability of vascular endothelial growth factor (*VEGF*) to augment the development of collateral arteries in vivo. In vitro studies have suggested that the use of *VEGF* also improves the endothelium-dependent relaxation of collaterals at the microvascular level. The purpose of this study was to determine in vivo the extent to which vasomotor responses of collateral microvessels are altered after *VEGF* treatment. METHODS AND RESULTS :Ischemia was induced in the hindlimb of 35 rats by excision of the femoral artery. Immediately thereafter, 400 microg of a plasmid encoding *VEGF* or ss-galactosidase (control) was transfected into limb muscles. Four weeks later, synchrotron radiation microangiography, with a spatial resolution of 30 microm, was performed to...

... endothelium-dependent vasodilator acetylcholine failed to induce dilation of collateral microvessels in control animals. By contrast, profound dilation of collaterals was observed after acetylcholine in *VEGF* -treated animals. This response was evident in vessels with a linear appearance but not in those with an undulating appearance. The resulting blood flow in...

... animals was only 64.6+/-17.0% of that of the contralateral normal limb, whereas blood flow was augmented to 106.1+/-8.4% in *VEGF*-treated animals ($P<0.05$). CONCLUSIONS: These results demonstrate in vivo that the use of *VEGF* restores impaired vasomotor responses in some types of collateral microvessels, which may help to provide a basis for understanding the microcirculation after therapeutic *angiogenesis* with *VEGF*.

5/3,K/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14034228 PMID: 9734840

Effect of time on the viability of ischemic skin flaps treated with vascular endothelial growth factor (*VEGF*) cDNA.

Taub P J; Marmur J D; Zhang W X; Senderoff D; Urken M L; Silver L; Weinberg H

Department of Otolaryngology, and Cardiovascular Institute, Mt. Sinai Medical Center, New York, NY 10029, USA.

Journal of reconstructive microsurgery (UNITED STATES) Aug 1998, 14 (6) p387-90, ISSN 0743-684X Journal Code: 8502670
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Effect of time on the viability of ischemic skin flaps treated with vascular endothelial growth factor (*VEGF*) cDNA.

... the efficacy of gene therapy on wound healing. The authors investigated whether delivery of the gene encoding a particular cytokine, known to be important in *angiogenesis*, could affect *ischemic* skin flaps. Anterior abdominal skin flaps, based solely on the epigastric artery and vein, were created in the Sprague-Dawley *rat* model. At the time of elevation, the arterial pedicle supplying each flap was infused either with the gene for vascular endothelial growth factor (*VEGF*) or physiologic saline alone. The flaps were resutured into place and observed for a period of either 4 or 3 days, at which time the...

... was measured by dye fluorescence. Tissue viability of the flaps was subsequently measured by planimetry after a period of 7 days. Flaps that received the *VEGF* gene and were ligated at 4 days had an average dye fluorescence index (DFI) of 31.1 following ligation, and 93.9 percent viable tissue...

... was 11.0 for the gene-infused group and 22.1 for the saline-infused group. The results suggest that delivery of the gene for *VEGF* can improve the survival of *ischemic* skin flaps, but that the effect of gene therapy is not limitless.

5/3,K/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14000590 PMID: 9701350
Reduction of *ischemic* damage by application of vascular endothelial growth factor in *rat* brain after transient *ischemia*.
Hayashi T; Abe K; Itoyama Y
Department of Neurology, Tohoku University School of Medicine Sendai, Japan.
Journal of cerebral blood flow and metabolism - official journal of the International Society of Cerebral Blood Flow and Metabolism (UNITED STATES) Aug 1998, 18 (8) p887-95, ISSN 0271-678X Journal Code: 8112566
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Reduction of *ischemic* damage by application of vascular endothelial growth factor in *rat* brain after transient *ischemia*.
Vascular endothelial growth factor (*VEGF*) is a secreted polypeptide and plays a pivotal role in *angiogenesis* in vivo. However, it also increases vascular permeability, and might exacerbate *ischemic* brain edema. The effect of this factor on the brain after transient *ischemia* was investigated in terms of infarct volume and edema formation, as well as cellular injury. After 90 minutes of transient middle cerebral artery occlusion, *VEGF* (1.0 ng/microL, 9 microL) was topically applied on the surface of the reperfused *rat* brain. A significant reduction of infarct volume was found in animals with *VEGF* application ($P < 0.001$) at 24 hours of reperfusion as compared with cases with vehicle treatment. Brain edema was significantly reduced in *VEGF* -treated animals ($P = 0.01$), and furthermore, extravasation of Evans blue was also decreased in those animals ($P < 0.01$). Terminal deoxynucleotidyl transferase-mediated dUTP...

... end labeling and immunohistochemical analysis for 70-kDa heat shock protein showed an amelioration of the stainings at 24 and 48 hours after reperfusion with *VEGF* treatment, which indicated reduction of neuronal damage. These results indicate that treatment with topical *VEGF* application significantly reduces *ischemic* brain damage, such as infarct volume, edema formation, and extravasation of Evans blue, and that the reductions were associated with that of neuronal injury.

5/3,K/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13982337 PMID: 9682821
Vascular endothelial growth factor expression in transient focal cerebral *ischemia* in the *rat*.
Cobbs C S; Chen J; Greenberg D A; Graham S H
Department of Neurosurgery, University of Alabama, Birmingham, USA.
Neuroscience letters (IRELAND) Jun 19 1998, 249 (2-3) p79-82, ISSN 0304-3940 Journal Code: 7600130
Document type: Journal Article

Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Vascular endothelial growth factor expression in transient focal cerebral *ischemia* in the *rat*.

Vascular endothelial growth factor (*VEGF*) has been implicated in hypoxia-induced *angiogenesis* in tumors and ischemia. We examined *VEGF* mRNA and protein expression after occlusion of the middle cerebral artery (MCA) in rats. *VEGF* mRNA expression studied by in situ hybridization was increased in the ischemic border zone 24 h after 30, 60 or 120 min of focal cerebral ischemia. *VEGF* protein expression measured by Western blots was also increased in this region 24 and 48 h after ischemia, and *VEGF* immunocytochemistry localized this increased expression to astroglia. Thus, *VEGF* is induced after focal cerebral ischemia and could have a role in pathophysiology and recovery in the ischemic border zone.

5/3,K/8 (Item 8 from file: 155)

13927118 PMID: 9626071

Mouse model of *angiogenesis*.

Couffinhal T; Silver M; Zheng L P; Kearney M; Witzenbichler B; Isner J M
Department of Medicine (Cardiology), St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston Massachusetts 02135, USA.

American journal of pathology (UNITED STATES) Jun 1998, 152 (6) p1667-79, ISSN 0002-9440 Journal Code: 0370502
Contract/Grant No.: HL02824; HL; NHLBI; HL40518; HL; NHLBI; HL57516; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Mouse model of *angiogenesis*.

Neovascularization of *ischemic* muscle may be sufficient to preserve tissue integrity and/or function and may thus be considered to be therapeutic. The regulatory role of vascular endothelial growth factor (*VEGF*) in therapeutic *angiogenesis* was suggested by experiments in which exogenously administered *VEGF* was shown to augment collateral blood flow in animals and patients with experimentally induced hindlimb or myocardial *ischemia*. To address the possible contribution of postnatal endogenous *VEGF* expression to collateral vessel development in *ischemia* tissues, we developed a *mouse* model of hindlimb *ischemia*. The femoral artery of one hindlimb was ligated and excised. Laser Doppler perfusion imaging (LDPI) was employed to document the consequent reduction in hindlimb blood ...

... detected in vivo. Endothelial cell proliferation was documented by immunostaining for bromodeoxyuridine injected 24 hours before each of these time points, providing additional evidence that *angiogenesis* constitutes the basis for improved collateral-dependent flow in this animal model. Neovascularization was shown to develop in association with augmented expression of *VEGF* mRNA and protein from skeletal myocytes as well as endothelial cells in the *ischemic* hindlimb; that such reparative *angiogenesis* is indeed dependent upon *VEGF* up-regulation was confirmed by impaired neovascularization after administration of a neutralizing *VEGF* antibody. Sequential characterization of the in vivo, histological, and molecular findings in this novel animal model thus document the role of *VEGF* as endogenous regulator of *angiogenesis* in the setting of tissue *ischemia* . Moreover, this murine model represents a potential means for studying the effects of gene targeting on nutrient *angiogenesis* in vivo.

5/3,K/9 (Item 9 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

13802032 PMID: 9500609

Vascular endothelial growth factor is essential for corpus luteum *angiogenesis*.

Ferrara N; Chen H; Davis-Smyth T; Gerber H P; Nguyen T N; Peers D; Chisholm V; Hillan K J; Schwall R H

Department of Cardiovascular Research, Genentech Inc., South San Francisco, California 94080, USA. Ferrara.Napoleone@gene.com

Nature medicine (UNITED STATES) Mar 1998, 4 (3) p336-40, ISSN 1078-8956 Journal Code: 9502015

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Vascular endothelial growth factor is essential for corpus luteum *angiogenesis*.

... of the ovarian corpus luteum (CL) are dependent on the growth of new capillary vessels. Although several molecules have been implicated as mediators of CL *angiogenesis*, at present there is no direct evidence for the involvement of any. Here we report the unexpected finding that treatment with truncated soluble Flt-1 receptors, which inhibit vascular endothelial growth factor (*VEGF*) bioactivity, resulted in virtually complete suppression of CL *angiogenesis* in a *rat* model of hormonally induced ovulation. This effect was associated with inhibition of CL development and progesterone release. Failure of maturation of the endometrium was also observed. Areas of *ischemic* necrosis were demonstrated in the corpora lutea (CLs) of treated animals. However, no effect on the preexisting ovarian vasculature was observed. These findings demonstrate that, in spite of the redundancy of potential mediators, *VEGF* is essential for CL *angiogenesis*. Furthermore, they have implications for the control of fertility and the treatment of ovarian disorders characterized by hypervascularity and hyperplasia.

5/3,K/10 (Item 10 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

13765640 PMID: 9462772

Vascular endothelial growth factor expression in expanded tissue: a possible mechanism of *angiogenesis* in tissue expansion.

Lantieri L A; Martin-Garcia N; Wechsler J; Mitrofanoff M; Raulo Y; Baruch J P

Department of Plastic Surgery, Henri Mondor Hospital, Paris XII University, Creteil, France.

Plastic and reconstructive surgery (UNITED STATES) Feb 1998, 101 (2) p392-8, ISSN 0032-1052 Journal Code: 1306050

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Vascular endothelial growth factor expression in expanded tissue: a possible mechanism of *angiogenesis* in tissue expansion.

Vascular endothelial growth factor (*VEGF*) is a major angiogenic growth factor. *Angiogenesis* stimulated by *VEGF* occurs in several important clinical contexts, including myocardial *ischemia*, retinal disease, and tumor growth. The level of *VEGF* is increased in several skin disorders and is stimulated by *ischemia*. Tissue expansion has been shown to induce *angiogenesis* and *ischemia* on the overlying skin. We therefore investigated the hypothesis that *VEGF* was expressed in expanded tissue. Three samples of skin were obtained from five patients who sustained reconstruction with tissue expansion. One sample was taken on...

... nonexpanded skin adjacent to the expanded area and one on the expanded skin on the site of expansion. On these samples we performed immunolocalization of *VEGF*. *Mouse* monoclonal antibody was used, recognized with rabbit anti-*mouse* immunoglobulin alkaline phosphatase-anti-alkaline phosphatase (APAAP) complex conjugated and revealed with naphthol red. Our results showed clearly an increased number of cells that fixated *VEGF* antibody on the site of expansion. Cell counts revealed that the numbers of cells expressing *VEGF* were statistically higher in expanded tissue than in nonexpanded tissue. Before expansion skin specimens did not express *VEGF*. These findings are the first to show the presence of a growth factor in expanded tissue. They open a new field of research on the biological explanation of tissue-expanded *angiogenesis*.

5/3,K/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13667532 PMID: 9377574
Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders.
Presta L G; Chen H; O'Connor S J; Chisholm V; Meng Y G; Krummen L; Winkler M; Ferrara N
Department of Immunology, Genentech, Inc., South San Francisco, California 94080, USA.
Cancer research (UNITED STATES) Oct 15 1997, 57 (20) p4593-9, ISSN 0008-5472 Journal Code: 2984705R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Vascular endothelial growth factor (*VEGF*) is a major mediator of *angiogenesis* associated with tumors and other pathological conditions, including proliferative diabetic retinopathy and age-related macular degeneration. The murine anti-human *VEGF* monoclonal antibody (muMAb *VEGF*) A.4.6.1 has been shown to potently suppress *angiogenesis* and growth in a variety of human tumor cells lines transplanted in nude mice and also to inhibit neovascularization in a *primate* model of *ischemic* retinal disease. In this report, we describe the humanization of muMAb *VEGF* A.4.6.1. by site-directed mutagenesis of a human framework. Not only the residues involved in the six complementarity-determining regions but also several framework residues were changed from human to murine. Humanized anti-*VEGF* F(ab) and IgG1 variants bind *VEGF* with affinity very similar to that of the original murine antibody. Furthermore, recombinant humanized MAb *VEGF* inhibits *VEGF*-induced proliferation of endothelial cells in vitro and tumor growth in vivo with potency and efficacy very similar to those of muMAb *VEGF* A.4.6.1. Therefore, recombinant humanized MAb *VEGF* is suitable to test the hypothesis that inhibition of *VEGF*-induced *angiogenesis* is a valid strategy for the treatment of solid tumors and other disorders in humans.

5/3,K/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13660496 PMID: 9354516
Vascular endothelial growth factor attenuates myocardial ischemia-reperfusion injury.
Luo Z; Diaco M; Murohara T; Ferrara N; Isner J M; Symes J F
Department of Surgery, St. Elizabeth's Medical Center, Tufts University School of Medicine, Boston, Massachusetts 02135-2997, USA.
Annals of thoracic surgery (UNITED STATES) Oct 1997, 64 (4) p993-8, ISSN 0003-4975 Journal Code: 15030100R
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed

BACKGROUND: Hypoxic endothelial cell activation plays a key role in the myocardial dysfunction resulting from *ischemia*-reperfusion injury. Recent evidence suggests that vascular endothelial growth factor (*VEGF*) may, in addition to promoting *angiogenesis* , modulate various aspects of endothelial function and repair. We examined whether administration of *VEGF* in the cardioplegic solution might have a beneficial effect on myocardial *ischemia*-reperfusion injury in an isolated *rat* heart model. METHODS: Hearts from Sprague-Dawley rats were perfused with Krebs-Henseleit solution in a modified Langendorff apparatus. Percent recovery of cardiac output, coronary flow, stroke work, and percent increase in coronary vascular resistance were measured after 2 hours of global *ischemia* and 40 minutes of reperfusion. Coronary effluent was collected after *ischemia* and reperfusion for measurement of creatine kinase. RESULTS: Hearts receiving cardioplegia solution containing 125 microg *VEGF* showed significantly improved recovery of cardiac output, coronary flow, and stroke work, and significantly reduced coronary vascular resistance compared with hearts receiving hyperkalemic cardioplegia only ($p < 0.05$). Coadministration of a nitric oxide synthase inhibitor attenuated the *VEGF* -induced cardiprotective effects. Hearts treated with *VEGF* released significantly less creatine kinase compared with control hearts. CONCLUSIONS: Addition of *VEGF* to hyperkalemic cardioplegia protects against myocardial *ischemia*-reperfusion injury in the isolated *rat* heart.

5/3,K/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13651680 PMID: 9342366

Intracerebral tumor-associated hemorrhage caused by overexpression of the vascular endothelial growth factor isoforms VEGF121 and VEGF165 but not VEGF189.

Cheng S Y; Nagane M; Huang H S; Cavenee W K
Ludwig Institute for Cancer Research, San Diego Branch, University of California at San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0660, USA.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Oct 28 1997, 94 (22) p12081-7, ISSN 0027-8424
Journal Code: 7505876
Contract/Grant No.: HL09391-02; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The vascular endothelial growth factor (*VEGF*) has been shown to be a significant mediator of *angiogenesis* during a variety of normal and pathological processes, including tumor development. Human U87MG glioblastoma cells express the three *VEGF* isoforms: VEGF121, VEGF165, and VEGF189. Here, we have investigated whether these three isoforms have distinct roles in glioblastoma *angiogenesis*. Clones that overexpressed each isoform were derived and inoculated into *mouse* brains. Mice that received VEGF121- and VEGF165-overexpressing cells developed intracerebral hemorrhages after 60-90 hr. In contrast, mice implanted with VEGF189-overexpressing cells had...

... vicinity of those tumors caused by cells overexpressing VEGF189, and none on the border of the tumors caused by the parental cells. Thus, by introducing *VEGF* -overexpressing glioblastoma cells into the brain, we have established a reproducible and predictable in vivo model of tumor-associated intracerebral hemorrhage caused by the enhanced expression of single molecular species. Such a model should be useful for uncovering the role of *VEGF* isoforms in the mechanisms of *angiogenesis* and for investigating intracerebral hemorrhage due to *ischemic* stroke or

congenital malformations.

5/3,K/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13512769 PMID: 9198238
***Angiogenesis* in embryos and ischemic diseases.**
Breier G; Damert A; Plate K H; Risau W
Department of Molecular Cell Biology, Max Planck Institute for Physiological and Clinical Research, Bad Nauheim, Germany. GBreier@kerckhoff.mpg.de
Thrombosis and haemostasis (GERMANY) Jul 1997, 78 (1) p678-83, ISSN 0340-6245 Journal Code: 7608063
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

***Angiogenesis* in embryos and ischemic diseases.**
Angiogenic growth factors and their endothelial receptors are thought to function as major regulators of blood vessel formation. Vascular endothelial growth factor (*VEGF*) and its receptors, Flt-1 (VEGFR-1) and Flk-1 (VEGFR-2), as well as Angiopoietin-1 and its receptor, Tie-2, represent key signal...

...development. The expression of these molecules correlates with phases of blood vessel formation during embryogenesis. Inactivation of any of the genes encoding these molecules in *mouse* embryos results in defective vascular development and embryonic lethality around mid-gestation. In addition, the *VEGF* signal transduction system has been implicated in the regulation of pathological blood vessel growth during certain *angiogenesis*-dependent diseases that are often associated with tissue *ischemia* , such as proliferative retinopathy or solid tumor growth. This hypothesis is substantiated by experiments, in which the inhibition of *VEGF* signal transduction resulted in the the inhibition of neovascularization in these diseases. Thus, the *VEGF* signal transduction system represents a useful target for an anti-angiogenic therapy.

5/3,K/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13415168 PMID: 9073561
Vascular endothelial growth factor is the major angiogenic factor in omentum: mechanism of the omentum-mediated *angiogenesis*.
Zhang Q X; Magovern C J; Mack C A; Budenbender K T; Ko W; Rosengart T K
Department of Cardiothoracic Surgery, New York Hospital-Cornell University Medical College, New York 10021, USA.
Journal of surgical research (UNITED STATES) Feb 1 1997, 67 (2) p147-54, ISSN 0022-4804 Journal Code: 0376340
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Vascular endothelial growth factor is the major angiogenic factor in omentum: mechanism of the omentum-mediated *angiogenesis*.
Omentum has been used clinically to promote wound healing and to stimulate the revascularization of *ischemic* tissues. The biologic mechanism responsible for these effects has, however, not yet been defined. A number of polypeptide growth factors that possess potent angiogenic properties...
... to determine whether one of these growth factors might be responsible for the angiogenic properties of the omentum. The levels of vascular

endothelial growth factor (*VEGF*) protein in a number of *rat* tissues and organs were analyzed by Western and enzyme immunoassay analysis. Because omentum was found to have the greatest *VEGF* concentrations of the tissues examined, antibody neutralization, transcription inhibition assays, and Northern blot analysis were performed under hypoxic and normoxic conditions on tissues extractions and primary tissue cultures of omentum to further characterize the functional significance of *VEGF* expression in these tissues. The omentum demonstrated the highest *VEGF* secretion rate as well as the highest concentration of *VEGF* protein of the various *rat* tissues and organs examined. Fractionation studies of the omentum furthermore demonstrated that omental adipocytes, rather than the stromal-vascular cells, were the primary source of *VEGF* protein. An endothelial cell mitogenic assay showed that a major portion of the mitogenic activity of heparin-binding proteins and conditioned media derived from omentum was abolished by *VEGF* antibody. Additional studies with the transcription inhibitor actinomycin-D furthermore demonstrated that the *VEGF* gene was continuously transcribed in the *rat* omental adipocytes. Incubation of the omental adipocytes under hypoxic conditions induced approximately a 1.7-fold increase in *VEGF* protein expression, which was abolished by actinomycin-D. Northern blot analysis demonstrated that hypoxia resulted in upregulation of the *VEGF* mRNA in the hypoxia-cultured omental adipocytes, suggesting that the augmentation of *VEGF* expression in omental adipocytes by hypoxia occurs at the transcriptional level. These data suggest that *VEGF* is the major angiogenic factor produced by omentum and possibly underlies the mechanism of omentum-induced *angiogenesis* . Augmented expression of *VEGF* by omental cells under hypoxic conditions may furthermore reflect the mechanism responsible for enhancing the angiogenic activity of omentum in the setting of *ischemia*.

5/3,K/16 (Item 16 from file: 155)

13164474 PMID: 8833917

Reactive oxygen intermediates increase vascular endothelial growth factor expression in vitro and in vivo.

Kuroki M; Voest E E; Amano S; Beerepoot L V; Takashima S; Tolentino M; Kim R Y; Rohan R M; Colby K A; Yeo K T; Adamis A P

Department of Surgery, Children's Hospital, Boston, Massachusetts 02115, USA.

Journal of clinical investigation (UNITED STATES) Oct 1 1996, 98 (7) p1667-75, ISSN 0021-9738 Journal Code: 7802877

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Elevated vascular endothelial growth factor (*VEGF*) levels are required for ocular and tumor *angiogenesis* in animal models. *Ischemic* hypoxia is strongly correlated with increased *VEGF* expression in these systems and is considered a physiologically relevant stimulus. Because *ischemic* hypoxia is often followed by reperfusion and reactive oxygen intermediate (ROI) generation, we examined the potential role of ROI in the control of *VEGF* gene expression. Human retinal pigment epithelial cells exposed to superoxide or hydrogen peroxide rapidly increased *VEGF* mRNA levels. Superoxide-associated mRNA increases were dose dependent, blocked by antioxidants, and associated with elevated *VEGF* protein levels in conditioned media. Increases in *VEGF* mRNA levels were also observed in cultured human melanoma and *rat* glioblastoma cells with superoxide or hydrogen peroxide. Cycloheximide prevented the ROI-associated increases in *VEGF* mRNA. Transcriptional inhibition with actinomycin D revealed an inducible increase in *VEGF* mRNA half-life, but nuclear run-on experiments showed no increase in *VEGF* transcriptional rate. Reoxygenation of human retinal pigment epithelial cells in vitro and ocular reperfusion in vivo increased retinal *VEGF* mRNA levels. Antioxidants prevented the reperfusion-associated *VEGF* mRNA increases in retina. We conclude that

ROIs increase *VEGF* gene expression in vitro and during the reperfusion of *ischemic* retina in vivo. The ROI-associated increases are mediated largely through increases in *VEGF* mRNA stability.

5/3,K/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13094468 PMID: 8761851
Effects of vascular endothelial growth factor on hemodynamics and cardiac performance.
Yang R; Thomas G R; Bunting S; Ko A; Ferrara N; Keyt B; Ross J; Jin H
Department of Cardiovascular Research, Genentech, South San Francisco, CA 94080, USA.
Journal of cardiovascular pharmacology (UNITED STATES) Jun 1996, 27 (6) p838-44, ISSN 0160-2446 Journal Code: 7902492
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Vascular endothelial growth factor (*VEGF*), a major regulator of *angiogenesis* , has therapeutic benefit in animal models of coronary or limb *ischemia*. However, the hemodynamic effects of *VEGF* have not been investigated. We examined the effects of *VEGF* on hemodynamics and cardiac performance. Mean arterial pressure (MAP), heart rate (HR), cardiac output, stroke volume, left ventricular (LV) dP/dt, and hematocrit were measured before and after intravenous injection of *VEGF* in conscious, instrumented rats. *VEGF* caused a dose-dependent reduction in MAP and an associated increase in HR. *VEGF* (250 micrograms/kg) significantly decreased cardiac output and stroke volume without affecting the inotropic state of the left ventricle, as determined by dP/dt. *VEGF* significantly increased hematocrit. Furthermore, *VEGF* did not affect contractility or HR in the isolated *rat* heart in vitro. The data suggest that the *VEGF*-induced decrease in cardiac output is due to reduced stroke volume, which may be caused by a decrease in venous return rather than a direct...

... pretreatment with N omega-nitro-L-arginine methyl-ester (L-NAME), a nitric oxide (NO) synthase inhibitor, significantly attenuated the depressor and tachycardic responses to *VEGF*, suggesting that *VEGF* -induced hypotension may be mediated by NO.

5/3,K/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12828919 PMID: 7586219
VEGF165 expressed by a replication-deficient recombinant adenovirus vector induces *angiogenesis* in vivo.
Muhlhauser J; Merrill M J; Pili R; Maeda H; Bacic M; Bewig B; Passaniti A ; Edwards N A; Crystal R G; Capogrossi M C
Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA.
Circulation research (UNITED STATES) Dec 1995, 77 (6) p1077-86, ISSN 0009-7330 Journal Code: 0047103
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

VEGF165 expressed by a replication-deficient recombinant adenovirus vector induces *angiogenesis* in vivo.
To evaluate the concept that localized delivery of angiogenic factors via virus-mediated gene transfer may be useful in the treatment of *ischemic* disorders, the replication-deficient adenovirus (Ad) vector AdCMV.VEGF165

(where CMV is cytomegalovirus and *VEGF* is vascular endothelial growth factor) containing the cDNA for human VEGF165, a secreted endothelial cell-specific angiogenic growth factor, was constructed. Human umbilical vein endothelial cells (HUVECs) and *rat* aorta smooth muscle cells (RASMCs) infected with AdCMV.VEGF165 (5 and 20 plaque-forming units [pfu] per cell) demonstrated *VEGF* mRNA expression and protein secretion into the supernatant. Furthermore, the conditioned medium from these cells enhanced vascular permeability in vivo. In contrast, neither *VEGF* mRNA nor secreted protein was found in uninfected HUVECs or RASMCs or in cells infected with the control vector AdCMV.beta gal (where beta gal...

... VEGF165 or AdCMV.beta gal (2 x 10(10) pfu) was resuspended in 0.5 mL Matrigel and injected subcutaneously into mice. Immunohistochemical staining demonstrated *VEGF* in the tissues surrounding the Matrigel plugs containing AdCMV.VEGF165 up to 3 weeks after injection, whereas no *VEGF* was found in the control plugs with AdCMV.beta gal. Two weeks after injection, there was histological evidence of neovascularization in the tissues surrounding the Matrigel containing AdCMV.VEGF165, whereas no significant *angiogenesis* was observed in response to AdCMV.beta gal. Furthermore, the Matrigel plugs with AdCMV.VEGF165 demonstrated hemoglobin content fourfold higher than the plugs with AdCMV...

...vivo studies are consistent with the concept that Ad vectors may provide a useful strategy for efficient local delivery of VEGF165 in the treatment of *ischemic* diseases.

5/3,K/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12822191 PMID: 7479819

Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (*VEGF*) using soluble *VEGF*-receptor chimeric proteins.

Aiello L P; Pierce E A; Foley E D; Takagi H; Chen H; Riddle L; Ferrara N; King G L; Smith L E

Beetham Eye Institute, Boston, MA, USA.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Nov 7 1995, 92 (23) p10457-61, ISSN 0027-8424 Journal Code: 7505876

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (*VEGF*) using soluble *VEGF*-receptor chimeric proteins.

The majority of severe visual loss in the United States results from complications associated with retinal neovascularization in patients with *ischemic* ocular diseases such as diabetic retinopathy, retinal vein occlusion, and retinopathy of prematurity. Intraocular expression of the angiogenic protein vascular endothelial growth factor (*VEGF*) is closely correlated with neovascularization in these human disorders and with *ischemia* -induced retinal neovascularization in mice. In this study, we evaluated whether in vivo inhibition of *VEGF* action could suppress retinal neovascularization in a murine model of *ischemic* retinopathy. *VEGF* -neutralizing chimeric proteins were constructed by joining the extracellular domain of either human (Flt) or *mouse* (Flk) high-affinity *VEGF* receptors with IgG. Control chimeric proteins that did not bind *VEGF* were also used. *VEGF* -receptor chimeric proteins eliminated in vitro retinal endothelial cell growth stimulation by either *VEGF* ($P < 0.006$) or hypoxic conditioned medium ($P < 0.005$) without affecting growth under nonstimulated conditions. Control proteins had no effect. To assess in vivo response, animals with bilateral retinal *ischemia* received intravitreal injections of *VEGF* antagonist in one eye and control protein

in the contralateral eye. Retinal neovascularization was quantitated histologically by a masked protocol. Retinal neovascularization in the eye ...

...Flt and Flk chimeric proteins with maximal inhibitory effects of 77% and 66%, respectively. No retinal toxicity was observed by light microscopy. These data demonstrate *VEGF*'s causal role in retinal *angiogenesis* and prove the potential of *VEGF* inhibition as a specific therapy for *ischemic* retinal disease.

5/3,K/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12611036 PMID: 7728992
Regulation of vascular endothelial growth factor in cardiac myocytes.
Levy A P; Levy N S; Loscalzo J; Calderone A; Takahashi N; Yeo K T; Koren G; Colucci W S; Goldberg M A
Cardiology Division, Brigham and Women's Hospital, Boston, MA 02115, USA.
Circulation research (UNITED STATES) May 1995, 76 (5) p758-66, ISSN 0009-7330 Journal Code: 0047103
Contract/Grant No.: DK-45098; DK; NIDDK; HL-46005; HL; NHLBI; T32-HL-07604; HL; NHLBI; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Collateral blood vessels supplement normal coronary blood flow and coronary blood flow compromised by coronary artery disease, thereby protecting the myocardium from *ischemia*. Collateral vessel formation is the result of *angiogenesis*. Vascular endothelial growth factor (*VEGF*), also known as vascular permeability factor (VPF), is a secreted mitogen specific for endothelial cells and an extremely potent angiogenic factor. In the present study, VPF/*VEGF* mRNA and protein were demonstrated to be markedly stimulated in primary *rat* cardiac myocytes in vitro in response to reduction of the oxygen tension to 1% or inhibition of the electron transport chain. Four isoforms of VPF/*VEGF* were coordinately regulated by hypoxia, including a novel isoform not previously described. Phorbol ester and the depolarizing agent veratridine, stimulators of protein kinase C and calcium influx, respectively, were found to markedly increase VPF/*VEGF* mRNA expression in cardiac myocytes. Forskolin, a potent stimulator of adenylate cyclase, produced a small but significant increase in VPF/*VEGF* mRNA expression in the cardiac myocytes. However, only H7, an inhibitor of protein kinase C, inhibited the hypoxic induction of VPF/*VEGF* mRNA; inhibitors of calcium influx and the calcium-calmodulin-dependent protein kinase II as well as inhibition of protein kinase A did not block the hypoxic induction of VPF/*VEGF* mRNA. This suggests that more than one signal transduction pathway is involved in regulating VPF/*VEGF* expression. The sensor that regulates the expression of hypoxia-responsive genes has been proposed to be a heme protein. Consistent with this model, transition metals...

5/3,K/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10279652 PMID: 7977826
Rapid induction of vascular endothelial growth factor expression by transient *ischemia* in *rat* heart.
Hashimoto E; Ogita T; Nakaoka T; Matsuoka R; Takao A; Kira Y
Fourth Department of Internal Medicine, School of Medicine, University of Tokyo, Japan.
American journal of physiology (UNITED STATES) Nov 1994, 267 (5 Pt 2) pH1948-54, ISSN 0002-9513 Journal Code: 0370511

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Rapid induction of vascular endothelial growth factor expression by transient *ischemia* in *rat* heart.
Vascular endothelial growth factor (*VEGF* or vascular permeability factor), a direct-acting, endothelial cell-specific mitogen, has been suggested to be involved in development and maintenance of vasculatures in tumor neovascularization and in normal tissues. To investigate possible roles of *VEGF* in ischemic hearts, we studied induction of *VEGF* mRNA by ischemia and hypoxia using coronary artery-ligated hearts in vivo and perfused hearts and cultured myocardial cells in vitro. *VEGF* mRNA was potently induced by ischemia in the heart in vivo. In perfused hearts, maximum expression was rapidly induced (within 30 min) by transient reversible...

... least 3 h. Induction was also caused by hypoxia, which was confirmed in perfused hearts and cultured myocardial cells. These results suggest that induction of *VEGF* mRNA is upregulated by oxygen deprivation in the heart and that not only infarction but also chronic ischemia in the clinical setting could induce *VEGF* as a potent *angiogenesis* factor to stimulate coronary collateral formation.

5/3,K/22 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011801409 BIOSIS NO.: 199900061069
Gene therapy for myocardial *angiogenesis*: Initial clinical results with direct myocardial injection of phVEFG165 as sole therapy for myocardial ischemia
AUTHOR: Losordo Douglas W; Vale Peter R; Symes James F; Dunnington Cheryl H ; Esakof Darryl D; Maysky Michael; Ashare Alan B; Lathi Kishor; Isner Jeffrey M (Reprint)
AUTHOR ADDRESS: St. Elizabeth's Medical Center, 736 Cambridge St., Boston, MA 02135, USA**USA
JOURNAL: Circulation 98 (25): p2800-2804 Dec. 22-29, 1998 1998
MEDIUM: print
ISSN: 0009-7322
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

Gene therapy for myocardial *angiogenesis*: Initial clinical results with direct myocardial injection of phVEFG165 as sole therapy for myocardial ischemia

ABSTRACT: Background- We initiated a phase I clinical study to determine the safety and bioactivity of direct myocardial gene transfer of vascular endothelial growth factor (*VEGF*) as sole therapy for patients with symptomatic myocardial *ischemia*. Methods and Results- *VEGF* gene transfer (GTx) was performed in 5 patients (all male, ages 53 to 71) who had failed conventional therapy; these men had angina (determined by angiographically documented coronary artery disease). Naked plasmid DNA encoding *VEGF* (phVEGF165) was injected directly into the *ischemic* myocardium via a mini left anterior thoracotomy. Injections caused no changes in heart rate (pre-GTx = 75 +- 15/min versus post-GTx = 80 +- 16/min...

...Ventricular arrhythmias were limited to single unifocal premature beats at the moment of injection. Serial ECGs showed no evidence of new myocardial infarction in any *patient*. Intraoperative blood loss was 0 to 50 cm3, and total chest tube drainage was 110 to 395 cm3. Postoperative cardiac output fell transiently but increased...

...03). Postoperative left ventricular ejection fraction (LVEF) was either unchanged (n=3) or improved (n=2, mean increase in LVEF=5%). Objective evidence of reduced *ischemia* was documented using dobutamine single photon emission computed tomography (SPECT)-sestamibi imaging in all patients. Coronary angiography showed improved Rentrop score in 5 of 5 patients. Conclusions- This initial experience with naked gene transfer as sole therapy for myocardial *ischemia* suggests that direct myocardial injection of naked plasmid DNA, via a minimally invasive chest wall incision, is safe and may lead to reduced symptoms and improved myocardial perfusion in selected patients with chronic myocardial *ischemia*.
DESCRIPTORS:
MISCELLANEOUS TERMS: myocardial *angiogenesis*

5/3,K/23 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0011354195 BIOSIS NO.: 199800148442
Microvessel development following therapeutic *angiogenesis* with vascular endothelial growth factor (*VEGF*) in a *rat* model of hindlimb *ischemia*
AUTHOR: Takeshita S; Isshiki T; Miyazawa Y; Eto K; Ochiai M; Tanaka E; Mori H; Sato T
AUTHOR ADDRESS: Dep. Med., Teikyo Univ. Hosp., Tokyo, Japan**Japan
JOURNAL: Journal of the American College of Cardiology 31 (2 SUPPL. A): p 104A-105A Feb., 1998 1998
MEDIUM: print
CONFERENCE/MEETING: 47th Annual Scientific Session of the American College of Cardiology Atlanta, Georgia, USA March 29-April 1, 1998; 19980329
SPONSOR: The American College of Cardiology
ISSN: 0735-1097
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

Microvessel development following therapeutic *angiogenesis* with vascular endothelial growth factor (*VEGF*) in a *rat* model of hindlimb *ischemia*
DESCRIPTORS:
MISCELLANEOUS TERMS: *angiogenesis*;

5/3,K/24 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0010298759 BIOSIS NO.: 199698766592
VEGF* expression in a *mouse* model of hind limb *ischemia
AUTHOR: Couffinhal T; Silver M; Witzenbichler B; Sheriff D D; Isner J M
AUTHOR ADDRESS: St. Elizabeth's Med. Center, Tufts Univ. Sch. Med., Boston, MA 02135, USA**USA
JOURNAL: FASEB Journal 10 (3): pA578 1996 1996
CONFERENCE/MEETING: Experimental Biology 96, Part II Washington, D.C., USA April 14-17, 1996; 19960414
ISSN: 0892-6638
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

VEGF* expression in a *mouse* model of hind limb *ischemia
DESCRIPTORS:
MISCELLANEOUS TERMS: *ANGIOGENESIS*;

5/3,K/25 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07529690 EMBASE No: 1999003076
Gene therapy for myocardial *angiogenesis*: Initial clinical results with direct myocardial injection of phVEGFinf 1inf 6$D5 as sole therapy for myocardial ischemia
Losordo D.W.; Vale P.R.; Symes J.F.; Dunnington C.H.; Esakof D.D.; Maysky M.; Ashare A.B.; Lathi K.; Isner J.M.
Dr. J.M. Isner, St. Elizabeth's Medical Center, 736 Cambridge St., Boston, MA 02135 United States
Circulation (CIRCULATION) (United States) 29 DEC 1998, 98/25 (2800-2804)
CODEN: CIRCA ISSN: 0009-7322
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 19

Gene therapy for myocardial *angiogenesis*: Initial clinical results with direct myocardial injection of phVEGFinf 1inf 6$D5 as sole therapy for myocardial ischemia

Background - We initiated a phase 1 clinical study to determine the safety and bioactivity of direct myocardial gene transfer of vascular endothelial growth factor (*VEGF*) as sole therapy for patients with symptomatic myocardial *ischemia*. Methods and Results - *VEGF* gene transfer (GTx) was performed in 5 patients (all male, ages 53 to 71) who had failed conventional therapy; these men had angina (determined by angiographically documented coronary artery disease). Naked plasmid DNA encoding *VEGF* (phVEGFinf 1inf 6$D5) was injected directly into the *ischemic* myocardium via a mini left anterior thoracotomy. Injections caused no changes in heart rate (pre- GTx = 75+/-15/min versus post-GTx = 80+/-16/min...

...Ventricular arrhythmias were limited to single unifocal premature beats at the moment of injection. Serial ECGs showed no evidence of new myocardial infarction in any *patient*. Intraoperative blood loss was 0 to 50 cmsup 3, and total chest tube drainage was 110 to 395 cmsup 3. Postoperative cardiac output fell transiently...

...03). Postoperative left ventricular ejection fraction (LVEF) was either unchanged (n=3) or improved (n=2, mean increase in LVEF=5%). Objective evidence of reduced *ischemia* was documented using dobutamine single photon emission computed tomography (SPECT)-sestamibi imaging in all patients. Coronary angiography showed improved Rentrop score in 5 of 5 patients. Conclusions - This initial experience with naked gene transfer as sole therapy for myocardial *ischemia* suggests that direct myocardial injection of naked plasmid DNA, via a minimally invasive chest wall incision, is safe and may lead to reduced symptoms and improved myocardial perfusion in selected patients with chronic myocardial *ischemia*.
MEDICAL DESCRIPTORS:
*heart muscle ischemia--surgery--su; *heart muscle ischemia--therapy--th; *
angiogenesis

5/3,K/26 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07389720 EMBASE No: 1998301254
Expression of vascular endothelial growth factor (*VEGF*) and its receptors (Flt-1 and Flk-1) following permanent and transient occlusion of the middle cerebral artery in the rat
Lennmyr F.; Ata K.A.; Funa K.; Olsson Y.; Terent A.
Dr. F. Lennmyr, Department of Medicine, University Hospital, S-751 85 Uppsala Sweden

Journal of Neuropathology and Experimental Neurology (J. NEUROPATHOL. EXP. NEUROL.) (United States) 1998, 57/9 (874-882)
CODEN: JNENA ISSN: 0022-3069
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 55

Expression of vascular endothelial growth factor (*VEGF*) and its receptors (Flt-1 and Flk-1) following permanent and transient occlusion of the middle cerebral artery in the rat

Vascular endothelial growth factor (*VEGF*) is a known endothelial mitogen and a potent enhancer of vascular permeability although its role in focal cerebral *ischemia* is still not completely understood. The present report describes the immunohistochemical distribution of *VEGF* and its 2 receptors, Flt-1 and Flk-1 at day 1 and 3 following permanent and transient middle cerebral artery occlusion (MCAO) in the *rat*. A bilateral increase in *VEGF* immunoreactivity, particularly in neurons and blood vessels, was seen in both the experimental designs by day 1. By day 3, the immunoreactivity was restricted chiefly to the lesion side, where reaction was most prominent in the border zones of the infarcts. Immunoreaction to *VEGF* was more pronounced in cases of permanent MCAO than in transient MCAO. Flt-1 reaction was increased in neurons, glial and endothelial cells after both...

...Immunoreactivity to Flk-1 was prominent in glial cells and was present to some extent in endothelial cells. These findings indicate an early upregulation of *VEGF* and its receptors after permanent as well as transient focal cerebral *ischemia* in the *rat*.
MEDICAL DESCRIPTORS:
protein expression; drug receptor binding; immunohistochemistry; blood vessel permeability; immunoreactivity; glia cell; endothelium cell; *angiogenesis*; receptor upregulation; hypoxia; brain ischemia; nonhuman; rat; animal experiment; animal model; controlled study; article; priority journal

5/3,K/27 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

07380372 EMBASE No: 1998285843
Increased vascular endothelial growth factor (*VEGF*) and transforming growth factorbeta (TGF(beta)) in experimental autoimmune uveoretinitis: Upregulation of *VEGF* without neovascularization
Vinores S.A.; Chan C.-C.; Vinores M.A.; Matteson D.M.; Chen Y.-S.; Klein D.A.; Shi A.; Ozaki H.; Campochiaro P.A.
S.A. Vinores, 825 Maumenee Building, Wilmer Ophthalmologic Institute, Johns Hopkins Univ. Sch. of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287-9289 United States
Journal of Neuroimmunology (J. NEUROIMMUNOL.) (Netherlands) 14 AUG 1998, 89/1-2 (43-50)
CODEN: JNRID ISSN: 0165-5728
PUBLISHER ITEM IDENTIFIER: S0165572898000757
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 59

Increased vascular endothelial growth factor (*VEGF*) and transforming growth factorbeta (TGF(beta)) in experimental autoimmune uveoretinitis: Upregulation of *VEGF* without neovascularization
...induced in Lewis rats and B10.A mice by immunization with S-antigen (S-Ag) to study the potential roles of vascular endothelial growth factor (*VEGF*) and the betainf 1 and betainf 2 isoforms of transforming growth factor (TGF(betainf 1) and TGF(betainf 2)) during the progression of the disease. *VEGF* has been implicated as an angiogenic factor in *ischemic* retinopathies; however, Lewis rats developing EAU have high levels of

VEGF in the retina, but no neovascularization. In the present study, immunohistochemical staining for *VEGF*, TGF(betainf 1) and TGF(betainf 2) was performed on the retinas of Lewis rats developing EAU or with oxygen-induced *ischemic* retinopathy. In rats immunized with S-antigen, a marked upregulation of *VEGF* was immunohistochemically visualized from the inner nuclear layer to the inner limiting membrane prior to blood-retinal barrier (BRB) failure and lymphocytic infiltration. *VEGF* is normally induced by hypoxia and its induction leads to neovascularization. Coincident with the increase in *VEGF*, there was increased immunoreactivity for TGF(betainf 1) and TGF(betainf 2) within the same layers of the retina. In contrast, rats with *ischemic* retinopathy and retinal neovascularization showed only a modest increase in *VEGF* immunoreactivity, which is largely confined to retinal ganglion cells and inner retinal vessels, and little or no increase in TGF(betainf 1) or TGF(betainf...
...addition, in mice developing EAU, which does not have an abrupt onset as it does in rats and may involve neovascularization, a comparable upregulation of *VEGF* in the inner retina to that seen in rats developing EAU occurs with no increase in TGF(betainf 1) or TGF(betainf 2). Since TGF(beta) can inhibit endothelial cell proliferation, it is likely that an increase in TGF(beta) may prevent *VEGF* from exerting its endothelial growth activity in the *rat* EAU model, but *VEGF* may be operative in inducing BRB failure. These data suggest that there is a complex interaction among growth factors in the retina and that retinal...
MEDICAL DESCRIPTORS:
retinitis--etiology--et; uveitis--etiology--et; autoimmune disease --etiology--et; *angiogenesis*; blood vessel permeability; retina blood vessel; retina neovascularization; immunohistochemistry; nonhuman; female; rat; animal model; controlled study; animal tissue; newborn; article; priority journal

5/3,K/28 (Item 4 from file: 73)

07148840 EMBASE No: 1998027211
Requirement for vascular endothelial growth factor in wound- and inflammation-related corneal neovascularization
Amano S.; Rohan R.; Kuroki M.; Tolentino M.; Adamis A.P.
A.P. Adamis, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114 United States
Investigative Ophthalmology and Visual Science (INVEST. OPHTHALMOL. VIS. SCI.) (United States) 1998, 39/1 (18-22)
CODEN: IOVSD ISSN: 0146-0404
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 28

PURPOSE. Vascular endothelial growth factor (*VEGF*) is required for vascular development and for *ischemia*-related tumor, iris, and retinal neovascularization. The role of *VEGF* in inflammatory corneal neovascularization is unknown and was investigated in these studies. METHODS. A *rat* model was used in which removal of the corneal and limbal epithelium resulted in circumferential neovascularization. Corneal *VEGF* mRNA levels were quantified with ribonuclease protection assays, and *VEGF* protein was studied in situ using immunohistochemical analysis. Controlled-release pellets containing anti-*VEGF* antibodies were implanted into the corneal stroma and were used to determine the requirement for *VEGF* in corneal neovascularization. RESULTS. *VEGF* mRNA and protein were induced to high levels after corneal injury and were temporally and spatially correlated with inflammation and neovascularization. *VEGF* immunoreactivity was localized primarily to the inflammatory cells invading the wounded cornea. The specific inhibition of *VEGF* bioactivity with neutralizing antibodies potently suppressed corneal neovascularization. CONCLUSIONS. These data are the first to demonstrate that *VEGF* may be required for inflammatory neovascularization of the *rat* cornea and to

identify *VEGF* as a functional endogenous corneal angiogenic factor.
MEDICAL DESCRIPTORS:
wound healing; cornea epithelium; *angiogenesis*; pathogenesis; nonhuman; rat; animal model; animal tissue; article; priority journal

5/3,K/29 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

07055146 EMBASE No: 1997336990
Intracerebral tumor-associated hemorrhage caused by overexpression of the vascular endothelial growth factor isoforms VEGFinf 1inf 2inf 1 and VEGFinf 1inf 6$D5 but not VEGFinf 1inf 8inf 9
Cheng S.-Y.; Nagane M.; Huang H.-J.S.; Cavenee W.K.
W.K. Cavenee, Ludwig Institute for Cancer Research, San Diego Branch, University of California, 9500 Gilman Drive, San Diego, CA 92093-0660 United States
Proceedings of the National Academy of Sciences of the United States of America (PROC. NATL. ACAD. SCI. U. S. A.) (United States) 1997, 94/22 (12081-12087)
CODEN: PNASA ISSN: 0027-8424
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 30

The vascular endothelial growth factor (*VEGF*) has been shown to be a significant mediator of *angiogenesis* during a variety of normal and pathological processes, including tumor development. Human US7MG glioblastoma cells express the three *VEGF* isoforms: VEGFinf 1inf 2inf 1, VEGFinf 1inf 6$D5, and VEGFinf 1inf 8inf 9. Here, we have investigated whether these three isoforms have distinct roles in glioblastoma *angiogenesis*. Clones that overexpressed each isoform were derived and inoculated into *mouse* brains. Mice that received VEGFinf 1inf 2inf 1- and VEGFinf 1inf 6$D5-overexpressing cells developed intracerebral hemorrhages after 60-90 hr. In contrast, mice...

...tumors caused by cells overexpressing VEGFinf 1inf 8inf 9, and none on the border of the tumors caused by the parental cells. Thus, by introducing *VEGF*-overexpressing glioblastoma cells into the brain, we have established a reproducible and predictable in vivo model of tumor-associated intracerebral hemorrhage caused by the enhanced expression of single molecular species. Such a model should be useful for uncovering the role of *VEGF* isoforms in the mechanisms of *angiogenesis* and for investigating intracerebral hemorrhage due to *ischemic* stroke or congenital malformations.
MEDICAL DESCRIPTORS:
angiogenesis; animal cell; article; controlled study; glioblastoma --etiology--et; growth regulation; human; human cell; molecular cloning; mouse; nonhuman; prediction; priority journal; reproducibility; species differentiation; vascular endothelium...

5/3,K/30 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

06315608 EMBASE No: 1995353353
VEGFinf 1inf 6$D5 expressed by a replication-deficient recombinant adenovirus vector induces *angiogenesis* in vivo
Muhlhauser J.; Merrill M.J.; Pili R.; Maeda H.; Bacic M.; Bewig B.; Passaniti A.; Edwards N.A.; Crystal R.G.; Capogrossi M.C.
Gerontology Research Center, National Institute on Aging, National Institutes of Health, 4940 Eastern Ave.,Baltimore, MD 21224 United States
Circulation Research (CIRC. RES.) (United States) 1995, 77/6 (1077-1086)

CODEN: CIRUA ISSN: 0009-7330
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

VEGFinf 1inf 6$D5 expressed by a replication-deficient recombinant adenovirus vector induces *angiogenesis* in vivo

To evaluate the concept that localized delivery of angiogenic factors via virus-mediated gene transfer may be useful in the treatment of *ischemic* disorders, the replication deficient adenovirus (Ad) vector AdCMV.VEGFinf 1inf 6$D5 (where CMV is cytomegalovirus and *VEGF* is vascular endothelial growth factor) containing the cDNA for human VEGFinf 1inf 6$D5, a secreted endothelial cell- specific angiogenic growth factor, was constructed. Human umbilical vein endothelial cells (HUVECs) and *rat* aorta smooth muscle cells (RASMCs) infected with AdCMV.VEGFinf 1inf 6$D5 (5 and 20 plaque-forming units (pfu) per cell) demonstrated *VEGF* mRNA expression and protein secretion into the supernatant. Furthermore, the conditioned medium from these cells enhanced vascular permeability in vivo. In contrast, neither *VEGF* mRNA nor secreted protein was found in uninfected HUVECs or RASMCs or in cells infected with the control vector AdCMV.betagal (where betagal is beta...

...D5 or AdCMV.betagal (2 x 10sup 1sup 0 pfu) was resuspended in 0.5 mL Matrigel and injected subcutaneously into mice. Immunohistochemical staining demonstrated *VEGF* in the tissues surrounding the Matrigel plugs containing AdCMV.VEGFinf 1inf 6$D5 up to 3 weeks after injection, whereas no *VEGF* was found in the control plugs with AdCMV.betagal. Two weeks after injection, there was histological evidence of neovascularization in the tissues surrounding the Matrigel containing AdCMV.VEGFinf 1inf 6$D5, whereas no significant *angiogenesis* was observed in response to AdCMV.betagal. Furthermore, the Matrigel plugs with AdCMV.VEGFinf 1inf 6$D5 demonstrated hemoglobin content fourfold higher than the plugs...
...consistent with the concept that Ad vectors may provide a useful strategy for efficient local delivery of VEGFinf 1inf 6$D5 in the treatment of *ischemic* diseases.
MEDICAL DESCRIPTORS:
**angiogenesis*; *neovascularization (pathology)

5/3,K/31 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE

06019986 EMBASE No: 1995050117
Vascular endothelial growth factor/vascular permeability factor expression in a mouse model of retinal neovascularization
Pierce E.A.; Avery R.L.; Foley E.D.; Aiello L.P.; Smith L.E.H.
Department of Ophthalmology, Children's Hospital, 300 Longwood Avenue,Boston, MA 02115 United States
Proceedings of the National Academy of Sciences of the United States of America (PROC. NATL. ACAD. SCI. U. S. A.) (United States) 1995, 92/3 (905-909)
CODEN: PNASA ISSN: 0027-8424
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

...the factors involved in the hypoxic neovascular response have not been fully identified. To investigate the role of vascular endothelial growth factor/vascular permeability factor (*VEGF*/VPF) in retinal neovascularization, the expression of *VEGF*/VPF mRNA and protein were studied in a *mouse* model of proliferative retinopathy. RNA (Northern) blot analysis revealed that retinal *VEGF*/VPF mRNA expression increased 3-fold between 6 and 12 hr of relative retinal hypoxia and remained elevated during the development of neovascularization. In situ hybridization localized *VEGF*/VPF mRNA to cells bodies in the inner nuclear layer of the retina. Immunohistochemical confocal microscopy demonstrated that *VEGF*/VPF protein levels increase with a time course

similar to that of the mRNA. The cells in the inner nuclear layer of the retina that produce *VEGF*/VPF were identified morphologically as Muller cells. These data suggest that *VEGF*/VPF expression in the retina plays a central role in the development of retinal *ischemia*- induced ocular neovascularization.
MEDICAL DESCRIPTORS:
angiogenesis; animal experiment; animal model; animal tissue; article; gene expression; hypoxia; immunohistochemistry; in situ hybridization; mouse; mueller cell; nonhuman; priority journal; proliferative retinopathy; protein analysis; retina...
?ds

```
Set     Items   Description
S1      81914   (ISCHEMIC OR ISCHEMIA) (S) (MAMMAL OR RODENT OR PRIMATE OR
             MOUSE OR RAT OR PATIENT)
S2        772   S1 AND (ANGIOGENESIS)
S3        318   S2 AND (VEGF)
S4         66   S3 NOT PY>1998
S5         31   RD (unique items)
?s s2 and (GM-CSF or G-CSF or M-CSF)
            772  S2
           2837  GM-CSF
           1043  G-CSF
            206  M-CSF
     S6       1  S2 AND (GM-CSF OR G-CSF OR M-CSF)
?t s6/3,k/all
```

6/3,K/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014766359 BIOSIS NO.: 200400133713
Surgical injection of autologous, G-CSF mobilized, peripheral blood CD133+ cells for myocardial regeneration in patients undergoing coronary artery bypass grafting.
AUTHOR: Pompilio Giulio (Reprint); Cannata Aldo (Reprint); Capogrossi Maurizio; Nascimbene Angelo (Reprint); Peccatori Fedro; Biglioli Paolo (Reprint); Martinelli Giovanni; Bertolini Francesco
AUTHOR ADDRESS: Cardiovascular Surgery and Gene-Cell Therapy, Cardiology "Monzino" Institute, Milan, Italy**Italy
JOURNAL: Blood 102 (11): p335a November 16, 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 45th Annual Meeting of the American Society of Hematology San Diego, CA, USA December 06-09, 2003; 20031206
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Bone-marrow stem cells are currently investigated as stimulators of myogenesis and *angiogenesis* in patients with a recent myocardial infarction, in candidates to coronary artery bypass grafting (CABG), or to induce *angiogenesis* in patients with refractory chronic angina not eligible for complete revascularization. Here we report a novel procedure for collection and surgical intramyocardial injection of peripheral...

...approved by the Institutional Board and patients signed an informed consent. After study enrollment, 10 microg/Kg/d G-CSF were administered sc to the *patient* for 4-5 days to mobilize PBPC. Twelve-leads electrocardiogram was obtained daily. PBPC were collected on day 4-5 by 3-4 h apheresis...

...repair, injections were accomplished along the border of the myocardial scar, directly visualized on the beating-heart. Conversely, when cell therapy was conducted to generate *angiogenesis*, cells were delivered into the chronically *ischemic* ungraftable myocardium, identified by

stress scintigraphy and 2-D ECG. We enrolled so far 4 patients. PBSC were intramyocardially delivered to repair a recent myocardial infarction (n=2) or injected in a large *ischemic* myocardial area not suitable for conventional revascularization (n=2). No cardiac or other complications were noted in early postoperative period or follow-up (3-9 m). In the two patients who underwent 5-m postoperative nuclear and angiographic reinvestigation, disappearance of both a previous inferior MI and a lateral wall *ischemia* were observed. Waiting for a longer follow-up in a larger series of patients, it is concluded that this novel approach of CABG and intramyocardial injection of blood-mobilized and purified CD133+ cells in a beating-heart is safe and feasible in patients with *ischemic* cardiomyopathy.
...REGISTRY NUMBERS: *G-CSF*
?ds

```
Set     Items   Description
S1      81914   (ISCHEMIC OR ISCHEMIA) (S) (MAMMAL OR RODENT OR PRIMATE OR
             MOUSE OR RAT OR PATIENT)
S2        772   S1 AND (ANGIOGENESIS)
S3        318   S2 AND (VEGF)
S4         66   S3 NOT PY>1998
S5         31   RD (unique items)
S6          1   S2 AND (GM-CSF OR G-CSF OR M-CSF)
?s s2 and (SCF or SDF-1)
            772  S2
           9517  SCF
            212  SDF-1
      S7      1  S2 AND (SCF OR SDF-1)
?t s7/3,k/all
```

7/3,K/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2004 BIOSIS. All rts. reserv.

0014765901 BIOSIS NO.: 200400133255
Few implanted bone marrow stem cells become endothelial and myocardial cells in ischemic myocardium in nonhuman primates.
AUTHOR: Yoshioka Toru (Reprint); Ageyama Naohide; Shibata Hiroaki; Yasu Takanori (Reprint); Takeuchi Koichi; Matsui Keiji (Reprint); Yamamoto Keiji (Reprint); Terao Keiji; Shimada Kazuyuki (Reprint); Ikeda Uichi; Ozawa Keiya; Hanazono Yutaka
AUTHOR ADDRESS: Department of Cardiology, Jichi Medical School, Minamikawachi, Tochigi, Japan**Japan
JOURNAL: Blood 102 (11): p213a November 16, 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 45th Annual Meeting of the American Society of Hematology San Diego, CA, USA December 06-09, 2003; 20031206
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: *Rodent* studies have shown that bone marrow stem cells implanted into the *ischemic* myocardium become endothelial and myocardial cells. A few clinical trials have suggested the possible use of bone marrow or mobilized peripheral blood stem cells for the treatment of cardiac *ischemia*. It is, however, unclear how implanted cells heal the heart. We have implanted genetically-marked bone marrow CD34+ cells into the *ischemic* myocardium in a nonhuman *primate* (cynomolgus macaque) model and tracked the in vivo fate of the cells. Cynomolgus bone marrow-CD34+ cells were collected and transduced twice within a day with simian immunodeficiency virus (SIV) vector encoding GFP (provided by DNAVEC Research Inc.) in the presence of *SCF*, Flt-3 ligand and thrombopoietin. On average 41% of the transduced cells expressed GFP at 48 hours after transduction. We have confirmed that one-day...

...is stable during in vitro differentiation to endothelial cells. Thus, GFP was expected to work as a good genetic tag after implantation. Cynomolgus acute myocardial *ischemia* was generated by ligating the left anterior descending artery. GFP-transduced autologous CD34+ cells (n=4) or saline (n=4) were injected into the *ischemic* border at 10 sites. Two weeks after the injection, the group receiving the cells demonstrated significantly improved regional blood flow as compared to the saline...

...echocardiography and colored microsphere. The cell-treated group also showed restored cardiac function and reduced infarct size. Histological examination revealed that capillary density of the *ischemic* region was significantly better preserved in the cell-treated group than in the saline-treated group. Endothelial cells derived from implanted cells were clearly detected in the *ischemic* region, as assessed by immunostaining of GFP and in situ PCR of the GFP gene. Implanted progeny, however, accounted for a small fraction (<1%) of...

...is mainly derived from host cells rather than from implanted progeny. In addition, implantation of CD34+ cells resulted in increased levels of VEGF in the *ischemic* region, implying that angiogenic cytokines secreted from implanted cells might play a primary role in therapeutic *angiogenesis*. On the other hand, implanted cell-derived myocardial cells were not detectable in the *ischemic* region. These data highlight an important species-specific difference between murine and nonhuman *primate* models for assessing in vivo stem cell plasticity.
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...*SCF* {stem cell factor
?ds

Set	Items	Description
S1	81914	(ISCHEMIC OR ISCHEMIA) (S) (MAMMAL OR RODENT OR PRIMATE OR MOUSE OR RAT OR PATIENT)
S2	772	S1 AND (ANGIOGENESIS)
S3	318	S2 AND (VEGF)
S4	66	S3 NOT PY>1998
S5	31	RD (unique items)
S6	1	S2 AND (GM-CSF OR G-CSF OR M-CSF)
S7	1	S2 AND (SCF OR SDF-1)

?s s2 and (angiopoitin-1 or angiopoietin-2 or (FLT-3 (w) ligand))

	772	S2
	0	ANGIOPOITIN-1
	537	ANGIOPOIETIN-2
	106	FLT-3
	284576	LIGAND
	0	FLT-3(W)LIGAND
S8	8	S2 AND (ANGIOPOITIN-1 OR ANGIOPOIETIN-2 OR (FLT-3 (W) LIGAND))

?rd
...completed examining records

S9	8	RD (unique items)

?t s9/3,k/all

9/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

15287024 PMID: 14576200

Cell type-specific regulation of angiogenic growth factor gene expression and induction of *angiogenesis* in nonischemic tissue by a constitutively active form of hypoxia-inducible factor 1.

Kelly Brian D; Hackett Sean F; Hirota Kiichi; Oshima Yuji; Cai Zheqing; Berg-Dixon Shannon; Rowan Ashley; Yan Zhijiang; Campochiaro Peter A; Semenza Gregg L
Program in Vascular Cell Engineering, Institute for Cell Engineering, Baltimore, Md, USA.

Circulation research (United States) Nov 28 2003, 93 (11) p1074-81, ISSN 1524-4571 Journal Code: 0047103

Contract/Grant No.: P01-HL65608; HL; NHLBI; R01-DK39869; DK; NIDDK; R01-HL55338; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Cell type-specific regulation of angiogenic growth factor gene expression and induction of *angiogenesis* in nonischemic tissue by a constitutively active form of hypoxia-inducible factor 1.

Understanding molecular mechanisms regulating *angiogenesis* may lead to novel therapies for *ischemic* disorders. Hypoxia-inducible factor 1 (HIF-1) activates vascular endothelial growth factor (VEGF) gene expression in hypoxic/*ischemic* tissue. In this study we demonstrate that exposure of primary cultures of cardiac and vascular cells to hypoxia or AdCA5, an adenovirus encoding a constitutively...

... repressed in response to hypoxia or AdCA5. In all cases, there was complete concordance between the effects of hypoxia and AdCA5. Injection of AdCA5 into *mouse* eyes induced neovascularization in multiple capillary beds, including those not responsive to VEGF alone. Analysis of gene expression revealed increased expression of ANGPT1, ANGPT2, platelet...

... growth factor-B, placental growth factor, and VEGF mRNA in AdCA5-injected eyes. These results indicate that HIF-1 functions as a master regulator of *angiogenesis* by controlling the expression of multiple angiogenic growth factors and that adenovirus-mediated expression of a constitutively active form of HIF-1alpha is sufficient to induce *angiogenesis* in nonischemic tissue of an adult animal.

; Adenoviridae--genetics--GE; Angiogenic Proteins--metabolism--ME; Angiopoietin-1--genetics--GE; Angiopoietin-1--metabolism--ME; *Angiopoietin-2*--genetics--GE; *Angiopoietin-2*--metabolism--ME; Animals; Cell Hypoxia--physiology--PH; Cells, Cultured; Eye--blood supply--BS; Eye--drug effects--DE; Fibroblasts--cytology--CY; Fibroblasts--drug effects--DE...

Chemical Name: Angiogenic Proteins; Angiopoietin-1; *Angiopoietin-2*; HIF1alpha protein; Pregnancy Proteins; Proto-Oncogene Proteins c-sis; RNA, Messenger; Transcription Factors; Vascular Endothelial Growth Factor A; product placenta growth factor

9/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12509274 PMID: 12963640

Impaired VE-cadherin/beta-catenin expression mediates endothelial cell degeneration in dilated cardiomyopathy.

Schafer Romana; Abraham Dietmar; Paulus Patrick; Blumer Roland; Grimm Michael; Wojta Johann; Aharinejad Seyedhossein

Laboratory for Cardiovascular Research, Department of Anatomy, University of Vienna, Vienna, Austria.

Circulation (United States) Sep 30 2003, 108 (13) p1585-91, ISSN 1524-4539 Journal Code: 0147763
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

... unknown. METHODS AND RESULTS: The myocardial expression of VE-cadherin/beta-catenin, Ang-1, Ang-2, and their receptor Tie-2 was examined in DCM, *ischemic* cardiomyopathy (ICM), and in control subjects through the use of real-time RT-PCR, Western blotting, and immunocytochemistry. EC degeneration was quantified by TEM. RNA...

... to examine the interplay between VEGF, VE-cadherin/beta-catenin, and Ang-2. Analysis of tissue sections with similar rates of EC degeneration in both *patient* groups showed that VE-cadherin/beta-catenin expression was

downregulated in DCM only (P<0.05). Although Ang-1 was not changed, Ang-2 expression...
; Adult; *Angiogenesis* Inducing Agents--metabolism--ME; *Angiopoietin-2* ; Cadherins--genetics--GE; Cardiomyopathy, Congestive--genetics--GE; Cells, Cultured; Coronary Vessels--ultrastructure--UL; Cytoskeletal Proteins --genetics--GE; Down-Regulation; Endothelial Growth Factors--pharmacology --PD...
Chemical Name: *Angiogenesis* Inducing Agents; *Angiopoietin-2*; Cadherins; Cytoskeletal Proteins; Endothelial Growth Factors; Intercellular Signaling Peptides and Proteins; Lymphokines; Trans-Activators; Vascular Endothelial Growth Factor A; Vascular Endothelial Growth Factors; cadherin ...

9/3,K/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12227454 PMID: 12571448
Temporal profile of *angiogenesis* and expression of related genes in the brain after ischemia.
Hayashi Takeshi; Noshita Nobuo; Sugawara Taku; Chan Pak H
Department of Neurosurgery, Program in Neurosciences, Stanford University School of Medicine, Stanford, California, USA.
Journal of cerebral blood flow and metabolism - official journal of the International Society of Cerebral Blood Flow and Metabolism (United States) Feb 2003, 23 (2) p166-80, ISSN 0271-678X Journal Code: 8112566
Contract/Grant No.: P50 NS 14543; NS; NINDS; R01 NS 25372; NS; NINDS; R01 NS36147; NS; NINDS; R01 NS38653; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Temporal profile of *angiogenesis* and expression of related genes in the brain after ischemia.
Angiogenesis is an intricately regulated phenomenon. Its mechanisms in the *ischemic* brain have not been clearly elucidated. The authors investigated expression of *angiogenesis* -related genes using a complementary DNA (cDNA) array method as well as Western blotting and immunohistochemistry, and compared these studies with a temporal profile of *angiogenesis* in *mouse* brains after *ischemia*. The number of vessels significantly increased 3 days after injury, and proliferating endothelial cells increased as early as 1 day. This means that *angiogenesis* occurs immediately after the injury. Ninety-six genes implicated in *angiogenesis* were investigated with a cDNA array study. It was found that 42, 29, and 13 genes were increased at 1 hour, 1 day, and 21...

... such as thrombospondins also increased. At 1 day, however, thrombospondins decreased to lower levels than in the control, indicating a shift from vascular protection to *angiogenesis*. At 21 days, many genes were decreased, but some involved in tissue repair were newly increased. Western blotting and immunohistochemistry showed findings compatible with the cDNA array study. Many molecules act in an orchestrated fashion in the brain after *ischemia* and should be taken into account for therapeutic *angiogenesis* for stroke.
; *Angiogenesis* Inducing Agents--metabolism--ME; Angiopoietin-1; *Angiopoietin-2*; Animals; Blood Vessels--pathology--PA; Brain--pathology --PA; Brain Ischemia--pathology--PA; Brain Ischemia--physiopathology--PP; Cerebrovascular Circulation; DNA, Complementary--genetics--GE; Endothelial Growth...
Chemical Name: Agpt protein, mouse; *Angiogenesis* Inducing Agents; Angiopoietin-1; *Angiopoietin-2*; DNA, Complementary; Endothelial Growth Factors; Intercellular Signaling Peptides and Proteins; Lymphokines; Membrane Glycoproteins; Thrombospondin 1; Vascular Endothelial Growth Factor A; Vascular Endothelial Growth Factors...

9/3,K/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11791918 PMID: 11978190

Expression of angiopoietin-2 and vascular endothelial growth factor in mice cerebral cortex after permanent focal cerebral ischemia.

Wang Ren-Gang; Zhu Xing-Zu

Department of Pharmacology, Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 200031, China.

Acta pharmacologica Sinica (China) May 2002, 23 (5) p405-11, ISSN 1671-4083 Journal Code: 100956087

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

... the expressions of vascular endothelial growth factor (VEG F), angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), Tie-1, and Tie-2 in C57BL/6 *mouse* brain after permanent focal cerebral *ischemia*. METHODS : The mRNA levels of VEGF, Ang-1, Ang-2, Tie-1, and Tie-2 were measured by semiquantitative reverse transcription polymerase chain reaction (RT...

... by immunohistochemistry. RESULTS : Low mRNA levels of VEGF, Ang-1, Ang-2, Tie-1, and Tie-2 were constitutively expressed in the normal cortex of *mouse*. After middle cerebral artery occlusion (MCAO), the expressions of VEGF, Ang-2, and Tie-2 mRNA were dramatically increased in the infarcted cortex and the elevation was remained through 7 d of *ischemia*. However, the levels of Ang-1 and Tie-1 mRNA were unchanged in the infarcted cortex. Immunoreactivities of Ang-2 or VEGF were hardly observed...

... and glial-like cells within the infarct core and perifocal area. CONCLUSION: The expressions of An g-2 and VEGF are induced after focal cerebral *ischemia*, which may contribute to the angiogenic response in the cortex of *ischemic* brain.

Descriptors: *Angiogenesis* Inducing Agents--biosynthesis--BI; *Cerebral Cortex--metabolism--ME; *Endothelial Growth Factors--biosynthesis--BI; *Infarction, Middle Cerebral Artery--metabolism--ME; *Intercellular Signaling Peptides and Proteins--biosynthesis...
; *Angiogenesis* Inducing Agents--genetics--GE; Angiopoietin-1; *Angiopoietin-2*; Animals; Endothelial Growth Factors--genetics--GE; Intercellular Signaling Peptides and Proteins--genetics--GE; Lymphokines --genetics--GE; Membrane Glycoproteins--biosynthesis--BI; Membrane Glycoproteins--genetics--GE...

Chemical Name: Agpt protein, mouse; *Angiogenesis* Inducing Agents; Angiopoietin-1; *Angiopoietin-2*; Endothelial Growth Factors; Intercellular Signaling Peptides and Proteins; Lymphokines; MEN1 protein, human; Membrane Glycoproteins; Neoplasm Proteins; Proto-Oncogene Proteins; RNA, Messenger; Receptors, Cell Surface...

9/3,K/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11645796 PMID: 11822892

Postischemic angiogenic factor expression in stroke-prone rats.

Wang Michael M; Klaus Judy A; Joh Hung-Dong; Traystman Richard J; Hurn Patricia D

Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21287, USA.

Experimental neurology (United States) Feb 2002, 173 (2) p283-8, ISSN 0014-4886 Journal Code: 0370712

Contract/Grant No.: NR03521; NR; NINR; NS20020; NS; NINDS; NS33668; NS; NINDS

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

... to experimental middle cerebral artery occlusion, and brain RNA was analyzed for expression of angiogenic genes. Expression of angiopoietin-2 increased after stroke in all *rat* strains and was significantly enhanced in SHRSP compared with control strains. In addition, expression of angiopoietin-1 and the angiopoietin receptor dropped markedly after stroke in SHRSP animals, but was not different after *ischemia* in SHR and WKY strains. Thus, the SHRSP brain elaborates a unique and specific pattern of angiopoietin system gene expression after stroke which may underlie...

Descriptors: *Angiogenesis* Inducing Agents--biosynthesis--BI; *Brain Ischemia--physiopathology--PP; *Genetic Predisposition to Disease; *Infarction, Middle Cerebral Artery--physiopathology--PP; *Proto-Oncogene Proteins; *Angiogenesis* Inducing Agents--genetics--GE; Angiopoietin-1; *Angiopoietin-2*; Animals; Blotting, Northern; Brain--blood supply--BS; Brain--metabolism--ME; Brain--pathology--PA; Brain Chemistry; Brain Ischemia--complications--CO; Brain Ischemia--pathology--PA; Disease...

Chemical Name: Agpt protein, rat; *Angiogenesis* Inducing Agents; Angiopoietin-1; *Angiopoietin-2*; MEN1 protein, human; Membrane Glycoproteins; Neoplasm Proteins; Proteins; Proto-Oncogene Proteins; RNA, Messenger

9/3,K/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11427381 PMID: 11524400

Implantation of bone marrow mononuclear cells into ischemic myocardium enhances collateral perfusion and regional function via side supply of angioblasts, angiogenic ligands, and cytokines.

Kamihata H; Matsubara H; Nishiue T; Fujiyama S; Tsutsumi Y; Ozono R; Masaki H; Mori Y; Iba O; Tateishi E; Kosaki A; Shintani S; Murohara T; Imaizumi T; Iwasaka T

Department of Medicine II and Cardiovascular Center, Kansai Medical University, Moriguchi, Osaka, Japan.

Circulation (United States) Aug 28 2001, 104 (9) p1046-52, ISSN 1524-4539 Journal Code: 0147763
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

BACKGROUND: Bone marrow implantation (BMI) was shown to enhance *angiogenesis* in a *rat* *ischemic* heart model. This preclinical study using a swine model was designed to test the safety and therapeutic effectiveness of BMI. METHODS AND RESULTS: BM-derived mononuclear cells (BM-MNCs) were injected into a zone made *ischemic* by coronary artery ligation. Three weeks after BMI, regional blood flow and capillary densities were significantly higher (4.6- and 2.8-fold, respectively), and ...

... cells in vitro and formed network structure with human umbilical vein endothelial cells. CONCLUSIONS: BMI may constitute a novel safety strategy for achieving optimal therapeutic *angiogenesis* by the natural ability of the BM cells to secrete potent angiogenic ligands and cytokines as well as to be incorporated into foci of neovascularization.

; Angiopoietin-1; *Angiopoietin-2*; Animals; Blotting, Northern; Cell Differentiation; Cell Line; Coronary Circulation; Endothelial Growth Factors--genetics--GE; Endothelium, Vascular--cytology--CY; Fibroblast Growth Factor 2--genetics--GE...

Chemical Name: Angiopoietin-1; *Angiopoietin-2*; Endothelial Growth Factors; Interleukin-1; Lymphokines; Membrane Glycoproteins; Proteins; RNA, Messenger; Tumor Necrosis Factor; Vascular Endothelial Growth Factor A;

Vascular Endothelial Growth Factors; angiopoietin...

9/3,K/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11106381 PMID: 11132088
Induction of *angiogenesis* related genes in the contralateral cortex with a rat three-vessel occlusion model.
Cheung W M; Chen S F; Nian G M; Lin T N
Division of Neuroscience, Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, ROC.
Chinese journal of physiology (China (Republic: 1949-)) Sep 30 2000, 43 (3) p119-24, ISSN 0304-4920 Journal Code: 7804502
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Induction of *angiogenesis* related genes in the contralateral cortex with a rat three-vessel occlusion model.
The bFGF/FGFR, VEGF/VEGFR and Angiopoietin/Tie receptor system are crucial for *angiogenesis* and vascular remodeling. With a *rat* focal cerebral *ischemia* model, we previously reported dramatic changes in the vascular density and *angiogenesis* related genes in the ipsilateral cortex after 60 minutes severe *ischemia* . While only a small increase in the capillary density was noted in the contralateral cortex with very mild *ischemia* . In the present study we further reported that only Tie-1 and VEGFR-2 mRNA were significantly changed in the contralateral cortex with a p...

... changes were very small. Interestingly, in contrast to a huge increase in the ipsilateral cortex, Tie-1 mRNA was slowly decreased after the onset of *ischemia* and stayed below the basal level throughout the remaining periods studied. The mechanism and significance for this decrease is not presently clear. In contrast to...

... ipsilateral cortex, the Angpo-1/Angpo-2 mRNA ratio was also slightly dropped below the basal level in the contralateral side in most of the *ischemia* -reperfusion periods studied, which is in line with the notion that small decrease in Angpo-1/Angpo-2 mRNA ratio implied small vascular remodeling activity...
; Angiopoietin-1; *Angiopoietin-2*; Animals; Blotting, Northern; Brain Chemistry--genetics--GE; Cerebrovascular Accident--physiopathology--PP; Endothelial Growth Factors--genetics--GE; Fibroblast Growth Factor 2 --genetics--GE; Gene Expression...
Chemical Name: Agpt protein, rat; Angiopoietin-1; *Angiopoietin-2*; Endothelial Growth Factors; Lymphokines; Membrane Glycoproteins; Proteins; RNA, Messenger; Receptors, Cell Surface; Receptors, Growth Factor; Vascular Endothelial Growth Factor A; Vascular Endothelial Growth Factors...

9/3,K/8 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014779258 BIOSIS NO.: 200400145919
Induction of functional neovascularization by whisker stimulation after focal ischemia.
AUTHOR: Whitaker V R (Reprint); Yu S P; Wei L (Reprint)
AUTHOR ADDRESS: Dept. Pathol and Lab. Med, Med. Univ. South Carolina, Washington Univ., St. Louis, MO, USA**USA
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2003 pAbstract No. 789.12 2003 2003
MEDIUM: e-file
CONFERENCE/MEETING: 33rd Annual Meeting of the Society of Neuroscience New

Orleans, LA, USA November 08-12, 2003; 20031108
SPONSOR: Society of Neuroscience
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Neurovascular plasticity is critical for long-term functional recovery after *ischemic* stroke. We previously showed microvascular proliferation and remodeling after local *ischemia* in the *rat* barrel cortex (Wei et al., 1997, 2001). We now hypothesize that neuroplasticity is a use-dependent process mediated by the TNFalpha pathway and test the idea by correlating whisker activity with the degree of *angiogenesis*, neurogenesis, and functional recovery after the barrel cortex stroke in mice.Adult mice of lacking TNFalpha receptors (p55-/-or p75-/-) were anesthetized and multiple branches...

...induction of VEGF, angiogenic receptors, and proliferating endothelia cells. VEGF, angiopoietin-1, angiopoietin-2, and NF-KAPPAB were expressed after 1-10 days of the *ischemia* insult in p75-/-mice, but not in p55-/-mice. Whisker stimulation increased Tie-1/Tie-2 and NF-KAPPAB expression in WT and p75-/-groups...

...functional recovery. The results suggest a relationship between the p55 receptor and the angiopoietin/Tie2 system; it is suggested that TNFalpha-NF-KAPPAB-cascade-induced *angiogenesis* promotes neurovascular plasticity and contributes to long-term functional recovery after barrel cortex stroke.
...REGISTRY NUMBERS: *angiopoietin-2*
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...*angiopoietin-2*
?ds

Set	Items	Description
S1	81914	(ISCHEMIC OR ISCHEMIA) (S) (MAMMAL OR RODENT OR PRIMATE OR MOUSE OR RAT OR PATIENT)
S2	772	S1 AND (ANGIOGENESIS)
S3	318	S2 AND (VEGF)
S4	66	S3 NOT PY>1998
S5	31	RD (unique items)
S6	1	S2 AND (GM-CSF OR G-CSF OR M-CSF)
S7	1	S2 AND (SCF OR SDF-1)
S8	8	S2 AND (ANGIOPOITIN-1 OR ANGIOPOIETIN-2 OR (FLT-3 (W) LIGAND))
S9	8	RD (unique items)

?s s2 and (hematopoietic (w) factor)

	772	S2
	128948	HEMATOPOIETIC
	2123114	FACTOR
	148	HEMATOPOIETIC(W)FACTOR
S10	0	S2 AND (HEMATOPOIETIC (W) FACTOR)

?logoff
23apr04 14:58:58 User259876 Session D613.2
$2.71 0.846 DialUnits File155
$5.88 28 Type(s) in Format 3
$5.88 28 Types
$8.59 Estimated cost File155
$7.28 1.300 DialUnits File5
$10.50 6 Type(s) in Format 3
$10.50 6 Types
$17.78 Estimated cost File5
$7.47 0.762 DialUnits File73
$18.90 7 Type(s) in Format 3
$18.90 7 Types
$26.37 Estimated cost File73
OneSearch, 3 files, 2.908 DialUnits FileOS
$3.24 TELNET
$55.98 Estimated cost this search

$56.32 Estimated total session cost 2.997 DialUnits

Status: Signed Off. (13 minutes)